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Applicants:	Webb, et al.
Serial No.:	09/265,307
Confirmation No.:	4390
Filing Date:	March 9, 1999
For:	FATTY ACID-ANTICANCER CONJUGATES AND USES THEREOF
Examiner:	B. Trinh
Art Unit:	1625

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Edward R. Gates

Commissioner for Patents
P.O. Box 1450
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Sir:

Response

The Examiner has indicated that claims 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, and 143-187 are allowable. The Examiner is thanked for this indication.

The Examiner has indicated that claims 28, 122, 127, 132-133, and 137-138 are objected to only as being dependent on a rejected base claim, but would be allowable if rewritten in independent form. The Examiner is thanked for this indication.

The Examiner has rejected claims 1, 5, 7, 12, 17, 21, 23, 33, 119-121, 123-126, 128-131, 134-136, 139-142, and 188-201 under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al, Kataoka et al, [or] Rentsch. Applicants respectfully disagree and request reconsideration in view of the declaration submitted herewith and in view of the following remarks.

As discussed in greater detain below, the cited references do not show or suggest the claimed invention. The only cited reference that presents comparative data on the MTD of a fatty acid conjugate versus the parent compound teaches away from the invention. The other references do not show any comparative data of MTD for a parent and a conjugate compound.

The MTD of a particular drug is entirely dependent on the route of administration of that drug. This was well known to those of ordinary skill in the art at the time of the present invention. (Dr. Balthasar, ¶14). The cited references do not teach or suggest the possibility of administering a fatty acid conjugate at a dosage above the MTD of the parent compound.

Kataoka et al show an experiment involving a fatty acid-anti cancer drug conjugate, N4-behenoyl-AraC. The conjugate is given at a dose of 100-1000mg/kg, IP. This is then contrasted

with the parent compound, AraC which was reported to be given at a dosage of 1600 mg/kg IP. Clearly, the conjugate was given at a **lower** dose than the parent compound (more than 70% lower on a molar basis).This is precisely the opposite of that required by the claims of the present invention.

The Examiner points out that Kataoka teaches that the conjugate releases the AraC over time. According to the Examiner, this would suggest to one of ordinary skill in the art that **more** AraC can be delivered on a molar basis as a conjugate. In particular, the Examiner states that the " conjugated drug has lower solubility in the body fluid and is released slowly to the body, thus a higher dose can be used and tolerated compared to the parent drug." It is believed that this view is contradicted by the Kataoka reference itself and by other prior art of record. As mentioned, Kataoka administered the conjugate at a lower does than the parent. Likewise, it is reportedly in U.S. Patent 6,291,690 that it would be expected that a conjugate of a fatty-acid and anticancer compound would be given at a lower does than the parent. In particular, that patent includes the statement that a lipid carrier should reduce "the rate at which the agent is cleared from the circulation of animals thereby meaning that less of the agent need be administered to achieve the desired therapeutic effect." Finally, as pointed out in the declaration submitted herewith, the Examiner's belief also is contradicted by the scientific literature.

Examples exist in the literature to demonstrate that slow release of anti-cancer drugs, where the time-course of drug circulation is prolonged, can actually decrease MTD. For example, in a review of phase I clinical studies with topotecan, Rowinsky and Verweij cited data showing that the MTD of topotecan is highly dependent on the mode of topotecan administration, ranging from 22.5 $mg/m^2/d$ when released into the body over 30 min, to 1 $mg/m^2/d$ when released into the body over 72 h (Rowinsky EK and Verweij J, Review of phase I clinical studies with topotecan, Seminars in Oncology, 24: S20-3-S20-10, 1997). Thus, **less** drug could be administered when the drug was administered more slowly.

A more recent example is found in the declarant's work teaching that slowing the time course of drug administration **decreases** MTD. Specifically, in recent work conducted in his laboratory (Lobo ED and Balthasar JP, Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice, Journal of Pharmaceutical Sciences, 92: 1654-1664, 2003), toxicity induced by methotrexate following intra-peritoneal administration in mice was investigated. The MTD of methotrexate was highly dependent on the time-course of release of the drug. For example, following administration of methotrexate by rapid ("bolus") injection, the authors found that MTD was 760 mg/kg. Following slow release of the dose from an osmotic pump over 72 hours, they found that MTD was dramatically reduced to 3.8 mg/kg. Again, **less** drug could be administered when the drug was administered more slowly.

Yoshida et al and Rentsch do not teach otherwise. In addition, these reference do not measure toxicity and make no showing whatsoever about the MTD of a parent compound versus a conjugate. It was well known at the time of the filing of the above patent application that the Maximum Tolerated Dose (MTD) of a specific drug depends on the mode of administration of that drug. Yoshida et al and Rentsch never made any measurement of the toxicity of the parent compound at all, let alone via the same mode of administration as the conjugate.

Yoshida et al. investigated the administration of a derivative of AraC, which was administered at doses ranging from 500mg/m^2 to 1300mg/m^2, in 10 patients diagnosed with non-Hodgkin's lymphoma. This was a very small study, where dose levels (500, 700, 900, and 1300 mg/m^2) were administered to groups of three patients on a 5-consecutive day schedule. The Yoshida et al. report did not investigate toxicity resulting from the administration of the parent compound (Ara-C). As such, there is no comparison of the maximum tolerated dose (MTD) of the conjugate versus Ara-C in this treatment group. Thus, Yoshida et al does not teach anything about the MTD of a conjugate versus a parent compound.

The treatment group of Yoshida et al, in addition, was heavily pre-treated, as Yoshida et al. state that the patients were "tolerant to conventional multiple medication treatment, and had experienced BH-AC treatment...in the past." This treatment group therefore would likely have a different MTD than for the normal patient population, and the MTD for this group was not measured or discussed. (Dr. Balthasar, ¶5&6) In fact, the MTD of Ara-C and BH-AC in such patients could be **dramatically** different than those in the normal patient population. Consequently, it is not appropriate to compare of the doses of BH-AC applied in the Yoshida et al. study (i.e., 500 – 1300 mg/m^2) to the maximum tolerated dose of Ara-C found in other groups of patients (i.e., that were not tolerant to multiple medication treatment, including past treatment with BH-AC).

Based on these facts, it is not possible to conclude from reading Yoshida et al. that fatty acid drug conjugates of Ara-C have a MTD exceeding that of Ara-C .

Rentsch et al. do not add anything to Yoshida et al. These authors, like Yoshida et al, did not investigate the development of toxicity following the administration of Ara-C and/or following administration of fatty acid conjugates of Ara-C. Consequently, the teachings of Rentsch et al. do not support the conclusion in the Office Action that the prior art demonstrates that fatty-acid anticancer conjugates allow "increases of the dosage of the conjugated drug without harming the body.

In view of the forgoing remarks and the declaration submitted herewith by Dr. Balthasar, an expert in the field of cancer pharmacokinetics and a consultant to Luitpold Pharmaceuticals, Inc, the present owner of the above identified patent application, it is respectfully requested that the rejection on the basis of 103 be withdrawn.

Respectfully submitted,

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